In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 10-398V
(To Be Published)

SHEA KYLIE SULLIVAN, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Special Master Corcoran Filed: February 13, 2015 Entitlement Decision; Human Papillomavirus ("HPV") Vaccine; Rheumatoid Arthritis ("RA"); Molecular Mimicry; Homology; Cumulative Effect

Sarah McIntee, Nelson Mullins Riley & Scarborough, LLP, Washington, DC, for Petitioner.

Alexis Babcock, U.S. Dep't of Justice, Washington, DC, for Respondent.

DECISION DENYING ENTITLEMENT[1]

On June 28, 2010, Shea Sullivan filed this action seeking compensation under the National Vaccine Injury Compensation Program (the "Vaccine Program"),[2] alleging that she incurred a variety of arthritis-like injuries after receipt of the Human Papillomavirus ("HPV") vaccine. Petition ("Pet.") (ECF No. 1) at 1, 3-4. After considering the record as a whole, and for the reasons explained below, I find that Petitioner has failed to carry her burden establishing causation, and therefore has not demonstrated entitlement to compensation under the Vaccine Program.

[1] Because this decision contains a reasoned explanation for my action in this case, it will be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, § 205, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2006)). As provided by 42 U.S.C § 300aa-12(d)(4)(B), however, the parties may object to the decision's inclusion of certain kinds of confidential information. To do so, Vaccine Rule 18(b) permits each party fourteen (14) days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the decision will be available to the public. *Id.*

[2] The National Vaccine Injury Compensation Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755 (codified as amended, 42 U.S.C.A. § 300aa-10 to 34 (2006)) [hereinafter "Vaccine Act" or "the Act"]. Individual section references hereafter will be to § 300aa of the Act.

I. Factual Background and Medical History

The record in this case consists of Ms. Sullivan's medical records, a daily self-health log she prepared, affidavits from her as well as her mother and father, the testimony of two experts, and medical or scientific literature submitted by the parties in support of their respective positions. I have reviewed the entire record as required by the Vaccine Act. In this ruling I address the sufficiency of Petitioner's evidence in support of an award of compensation.

A. Petitioner's Medical History

Petitioner was nearly sixteen years old at the time she received her first Gardasil[3] vaccination (part of a series of three vaccinations) on June 27, 2007, during a wellness visit to the Pediatric and Adult Medicine Clinic in Tustin, California. Pet'r's Ex. 5 at 54-55; Pet'r's Ex. 2 at 2 (birth certificate); Pet'r's Ex. 3 at 2 (vaccination record). Overall, Ms. Sullivan was assessed at the time as a "well adolescent." Pet'r's Ex. 5 at 55.

On August 10, 2007, Ms. Sullivan's mother contacted Valerie Kozak, M.D. (Petitioner's primary care physician) at Pediatric and Adult Medicine to report that Petitioner appeared to be suffering from heart palpitations. Pet'r's. Ex. 5 at 55. Ms. Sullivan was apparently seen again on August 29, 2007, when she received her second Gardasil vaccination. Pet'r's Ex. 3 at 3. There are no subsequent records of any medical visits between August 27, 2007, and the time Petitioner received her third Gardasil vaccination on January 4, 2008. Pet'r's Ex. 5 at 56.

On February 11, 2008, Ms. Sullivan's mother called Dr. Kozak, this time to report that Petitioner was suffering from a sore throat, headache, and abdominal pain, and Dr. Kozak prescribed an antibiotic. Pet'r's Ex. 5 at 56. Ms. Sullivan was not seen again by a physician until April 18, 2008 (fifteen weeks after receiving her third Gardasil vaccination), when she reported experiencing left knee pain over the prior one to two weeks. *Id*. at 57. In the relevant medical history, it was noted that Petitioner ran track at school. *Id.* On examination, Ms. Sullivan's left knee proved to be tender medially and in the patella (knee cap) region, but she had full range of motion and the knee was otherwise stable, so she was merely referred to orthopedics for an evaluation (although the medical records do not indicate whether she followed through with the evaluation). *Id.*

Months later, Ms. Sullivan went back to Dr. Kozak for a follow-up visit in October of 2008 regarding the knee pain that she had been experiencing as well as swelling in her hands, feet, and forearms. Pet'r's Ex. 5 at 56. The possibility of arthritis as an explanation for Petitioner's symptoms is recorded in the medical history from this visit. *Id.* Laboratory studies showed normal comprehensive

[3] Gardasil is a quadrivalent recombinant vaccine (meaning it is made from genetically engineered material but does not contain live viruses) manufactured from the L1 protein of four strains of HPV (strains 6, 11, 16, and 18). *See generally* Gardasil Package Insert, *available at* http://www.fda.gov/BiologicsBloodVaccines/ Vaccines/ ApprovedProducts/UCM094042.

metabolic panel ("CMP"), complete blood count ("CBC"), and urinalysis results. *Id*. at 58-63. An antinuclear antibody ("ANA") screen, double–stranded DNA, smooth muscle antibody, C3 complement, cardiolipin antibodies, thyroid function, and direct antiglobulin tests were also negative for abnormalities. *Id.*

Ms. Sullivan subsequently saw Eric Wei En Lee, M.D. at Orange Orthopedic Medical Group in Orange, California on October 21, 2008, for an orthopedic evaluation. Pet'r's Ex. 7 at 6-8. As the treatment records from that visit indicate, Petitioner reported that her onset of symptoms had occurred in April 2008 "while running track." *Id*. at 6. She also related to Dr. Lee that she had experienced another episode of pain while running on the beach during the same period, and characterized the pain as constant and severe. *Id.* She specifically reported "objective instability, mechanical popping clicking, weakness, and decreased range of motion." *Id.* A physical examination performed on Petitioner revealed "peripheral joint stiffness." *Id*. at 7. An examination of her knee in particular revealed no erythema, swelling, drainage, or sign of infection; other aspects of her exam also had normal results, although there was a 1+ effusion and abnormalities with the patellar exam. *Id*. Dr. Lee diagnosed Ms. Sullivan with a patellofemoral chondromalacia (damage to the patella) and malalignment, as well as mild flexible pes planus (flat feet). *Id.*

Ms. Sullivan underwent an MRI of her knee on October 22, 2008, which showed intact menisci, tendons, and ligaments. Pet'r's Ex. 7 at 10. A moderate amount of joint effusion was observed (although its etiology was unclear). *Id*. She returned to Dr. Lee's clinic for follow-up on October 29, 2008, at which time (taking into account the MRI) she was again diagnosed with left knee patellofemoral chondromalacia, leading Dr. Lee to recommend physical therapy. *Id.* at 11, 12.

On November 3, 2008, Ms. Sullivan presented to Scott Graham, M.D. at South County Orthopedic Specialists in Laguna Woods, California for a second opinion regarding her left knee pain. Pet'r's Ex. 8 at 6-7. She again reported that her pain had existed since April of 2008 after "running on the beach," and although she could not remember if there had been a specific injury, she did recall having pain and swelling the next day. *Id*. The medical records from that visit note that Petitioner's family history was significant for arthritis, diabetes, cancer, and stroke. *Id.* at 6. A physical examination showed left knee swelling and tenderness, without warmth, but Petitioner nevertheless demonstrated a full range of motion and no hip irritability. *Id.* Dr. Graham reviewed the imaging studies and agreed that they were normal except for the presence of effusion. *Id.* He diagnosed Ms. Sullivan with a possible occult medial meniscal tear, and gave her a cortisone injection. *Id.* at 7. There was no mention of vaccination in Petitioner's treatment records from this visit, nor was Gardasil, or any other vaccine, identified as a possible cause of Ms. Sullivan's injuries.

Petitioner had a follow-up visit with Dr. Graham on December 1, 2008. Pet'r's Ex. 8 at 11. Because she continued to report knee pain despite the cortisone injection she had received in November, surgical intervention was recommended. *Id*. Ms. Sullivan subsequently underwent arthroscopic knee surgery performed by Dr. Graham on December 16, 2008. *Id.* at 12-13. Her post-operative diagnoses

were: (1) medial compartmental synovitis scar tissue, (2) lateral tibial plateau grade III chondral fissure, and (3) suprapatellar plica; follow-up physical therapy was recommended. *Id.* at 21-24. Ms. Sullivan underwent physical therapy treatments at Knight Physical Therapy in Anaheim, California, but not consistently, and she did not complete all of her sessions. *See* Pet'r's Ex. 9 at 2-9. At a session on February 2, 2009, she was noted to be doing well overall, although her knee was more swollen than usual due to standing for an extended period of time at a recent concert, and she was urged to keep up with her therapy. *Id*. at 11.

On February 11, 2009, Ms. Sullivan was seen by Dr. Graham for a post-surgery follow-up. Pet'r's Ex. 8 at 26. Petitioner now reported that although her knee pain had improved, she was experiencing pain in multiple joints. *Id.* She thereafter went back to Dr. Kozak on April 6, 2009 (a year after she claims to have first experienced knee pain) with complaints of joint pain in her arms and hands, as well as a new kind of knee pain different from what she had previously experienced. Pet'r's Ex. 5 at 63. It was now noted (for the first time in the medical records) that Ms. Sullivan "associates [her symptoms] with HPV vaccine." *Id*. The contemporaneous medical records specifically note that Petitioner had looked up information regarding the connection between the Gardasil vaccination and rheumatoid arthritis ("RA") on the internet and reported having found five cases associated with a class action lawsuit regarding the vaccine. *Id.*

Ms. Sullivan returned to Dr. Kozak on July 13, 2009. Pet'r's Ex. 5 at 64. By this time, Petitioner reported that she had been diagnosed with "inflammatory" arthritis "per rheumatology" (*id.*), presumably referring to the assessment of Thomas R. Powell, M.D., a rheumatologist in Orange, California, who saw Petitioner that same month. *See generally* Pet'r's Ex. 10. She later saw Dr. Kozak again in August, at which time she repeated her concern that the Gardasil vaccine was the cause of her arthritic condition. Pet'r's Ex. 5 at 65. As a written phone record from August 3, 2009, indicates, Dr. Kozak informed Ms. Sullivan's mother that there were no scientific articles linking the Gardasil vaccine to arthritis. *Id*. Laboratory work performed by Dr. Powell showed that Ms. Sullivan's cyclic citrullinated peptide antibody ("CCP") (the presence of which is strongly associated with RA) was elevated, while serum protein electrophoresis, rheumatoid factor ("RF"), ANA, CBC, and CMP results were normal. Pet'r's Ex. 10 at 3-9.

On September 9, 2009, Petitioner was seen by William Shiel, M.D., FACP, FACR, at Mission Internal Medicine Group, Inc. in Mission Viejo, California for a rheumatologic evaluation. Pet'r's Ex. 11 at 1-3. A physical examination was significant for hyperhydrosis of the feet, swollen proximal interphalangeal ("PIP") joints with decreased flexion, swollen wrists, trace swelling of the knees with decreased flexion to 120 degrees, and tender metatarsophalangeal ("MTP") joints. *Id*. at 2-3. Ms. Sullivan's erythrocyte sedimentation rate (a test used to measure the degree of inflammation present) was slightly elevated at thirty-two. *Id.* 5-7. RF and ANA tests were negative, while her anti-CCP antibody was strongly positive. *Id.* Petitioner was diagnosed with symmetric polyarthritis, based on such test results and the generally-observed loss of range of motion of the wrists and PIP joints. *Id*. at 4.

Dr. Shiel ultimately felt that Ms. Sullivan's symptoms were very suggestive of RA, and recommended a number of medications to treat her symptoms. *Id.*

At a follow–up visit with Dr. Shiel on September 25, 2009, Ms. Sullivan complained of "[p]ain all over the joints for [two] years" and was started on medication to treat her symptoms. Pet'r's Ex. 11 at 10. Imaging studies included a normal bilateral wrist x-ray series, hand x-rays that showed mild periarticular osteopenia, and foot x-rays that showed periarticular osteopenia. *Id*. at 11-14. Petitioner was thereafter formally diagnosed by Dr. Kozak as suffering from Juvenile Rheumatoid Arthritis ("JRA").[4] Pet'r's Ex. 5 at 68. An addendum from Ms. Sullivan's primary care physician on May 19, 2010, stated that she continued to have achy joints and shoulders, and swollen fingers, but her medications had alleviated some of her symptoms. *Id.* at 69. Those same records note concerns about why Petitioner was "ill" so frequently but offer no explanation. *Id.*

B. Expert Testimony

1. *Dr. Richard Roseff* – Petitioner's expert, Richard Roseff, M.D., graduated from Boston University School of Medicine in 1980 (after completing his undergraduate degree at Amherst College). Tr. at 5; ECF No. 12-1 at 3. Dr. Roseff went on to complete his residency at Boston Medical Center, followed by a two-year fellowship in rheumatology at Massachusetts General Hospital. Tr. at 5. Dr. Roseff is board certified in internal medicine and rheumatology but not in pediatric rheumatology. *Id.* at 6, 43. He is currently a member of the American College of Rheumatology, and he has a rheumatology sub-specialty private practice in Connecticut. *Id*. at 7. Dr. Roseff has lectured on RA, but he has not published any articles on this topic. *Id.* Dr. Roseff is also not an immunologist, epidemiologist, or toxicologist, and he has no personal expertise in the subject of vaccine causation. *Id.* at 80, 136-38.

Dr. Roseff's opinion is based on his review of Petitioner's medical records, affidavits (from Petitioner as well as her parents), and medical or scientific literature (including articles on vaccine-induced autoimmune illness as well as articles on the latency period[5] between vaccination and the development of autoimmune diseases). Tr. at 12. It is not part of Dr. Roseff's regular practice to see individuals who are under eighteen years of age (as Ms. Sullivan was at the time of her diagnosis). *Id.* at 43. Additionally, Dr. Roseff could not recall having diagnosed anyone with a vaccine-related arthritic condition as part of his clinical practice. *Id*. at 76.

[4] As both parties' experts agreed, rheumatoid conditions that begin when a patient is sixteen are typically not classified as juvenile, according to relevant diagnostic criteria. Tr. at 88, 92, 94. Therefore, although Dr. Kozak formally diagnosed Ms. Sullivan with JRA (presumably due to her young age at the time of onset of her symptoms), there is no dispute in this case that RA was the proper diagnosis (*see, e.g.*, Tr. at 66, 94), and I accept it as such for purposes of this decision.

[5] Dr. Roseff defined latency period to be the asymptomatic period following exposure. Tr. at 133.

Dr. Roseff's opinion began with testimony about RA, which he characterized as an "inflammatory polyarthritis of unclear etiology." Pet'r's Expert Report dated Feb. 2, 2011 at 3 [hereinafter "Roseff Report"]; *see also* Tr. at 10. As Dr. Roseff explained, RA has several patterns of onset, but classically results in a symmetric (meaning bilateral) inflammation of joints associated with stiffness and pain that, if left untreated or treated inadequately, can result in disability and even mortality. Tr. at 10. The majority of individuals who develop RA fall into the same demographic as Petitioner (*i.e.*, young adult females), although Dr. Roseff later clarified that he believed Ms. Sullivan fell on the younger end of that spectrum. *Id.* at 10-11.

Dr. Roseff acknowledged that certain hereditary and environmental factors may place an individual at higher risk for developing RA (Tr. at 2), and that Ms. Sullivan's illness could have been caused by such non-vaccine related factors. Addendum to Pet'r's Expert Report, dated Feb. 9, 2011 (ECF No. 12-3) at 2 [hereinafter "Roseff Amended Report"]. However, Dr. Roseff opined that it was unlikely that Petitioner's RA could be attributed to this type of random occurrence. Tr. at 17. He initially reached this conclusion after reading various reports from the Gardasil Vaccine Adverse Event Reporting ("VAERS") database concerning the experiences of other individuals who developed RA after receiving the Gardasil vaccine – suggesting to him a correlation between the two. *Id*. at 18. He later admitted, however, that the VAERS database is a passive reporting system permitting anyone to report an adverse event, regardless of whether a medical professional has concluded that the adverse event can be linked to vaccination. *Id.* at 46.

As additional support for his causation opinion, Dr. Roseff pointed to findings from clinical studies included in the Gardasil vaccine package insert, which indicated that of the 9,412 individuals receiving placebo, two developed RA, while of 10,706 individuals who had received Gardasil, six developed this condition. Roseff Report at 3. Dr. Roseff characterized such numbers as a "disturbing trend," while admitting that they were nevertheless small and not otherwise corroborated by any statistical evidence from any specific scientific or medical studies regarding the Gardasil vaccine (or even the HPV vaccine more generally). *Id.* at 3, 8.

Dr. Roseff opined that because various viral antigens have been implicated in the development of RA, "[b]y extension, it is reasonable to suppose that immunizations can also be potential environmental triggers for RA development." Roseff Report at 3. As evidence of this concept, Dr. Roseff asserted that "[i]t had been known for years that exposure to the rubella vaccine represents a causal link to a chronic arthritis *resembling* RA in a small percentage of patients." *Id.* (emphasis added). Dr. Roseff also cited an article[6] involving an attempt to link human parvovirus B19 to development of RA and acute inflammatory arthritis in genetically predisposed individuals. Tr. at 21-22. Although no studies have linked the wild HPV virus to the development of RA, Dr. Roseff testified that the vaccine

[6] B. J. Cohen, M. M. Buckley, J. P. Clewley, V. E. Jones, A. H. Puttick & R. K. Jacoby, *Human Parvovirus Infection in Early Rheumatoid and Inflammatory Arthritis*, 45 Annals of Rheumatic Diseases 832 (1986) (Pet'r's Ex. 37).

was different because an individual is exposed to four strains of HPV all at once – meaning that the vaccinated individual is "getting a pretty heavy dose of the papilloma virus." *Id.* at 77-78.

For the precise mechanism by which the Gardasil vaccine could result in the development of RA, Dr. Roseff proposed molecular mimicry. Tr. at 76. Under Dr. Roseff's theory, (a) components of the Gardasil vaccine present to the body an antigen,[7] (b) resulting in an immune response (the development of B cell lymphocytes), (c) which in turn produce antibodies to the viral sequences in the vaccination that will in the future protect the body from a wild HPV infection. The body, however, may also have homologous protein sequences that will also be attacked by the same antibodies, thereby resulting in the onset of autoimmunity (where the body is attacking its own tissue).[8] *Id.* at 76-77. In reaching this conclusion that the Gardasil vaccination could cause cross-reactions leading to the onset of autoimmunity, Dr. Roseff relied on Kanduc, D., *Penta- and Hexapeptide Sharing Between HPV16 and Homo Sapiens Proteomes,* 1 Int'l J. Med. and Med. Sci. 383, 386-87 (Sept. 2009) (ECF No. 65-3) (Pet'r's Ex. 36) [hereinafter "Kanduc"], which examined the cross-reactivity potential of HPV-16 (one of the strains of HPV included in the Gardasil vaccination) and finding that it shares thousands of identical peptide motifs with human proteomes.[9] Kanduc at 386. Dr. Roseff opined that, based on Kanduc, there is likely sufficient homology between the viral components of the Gardasil vaccine and human proteins for the development of autoimmune illness. Tr. at 19-20.

Dr. Roseff also proposed an alternative mechanism for how the Gardasil vaccine could produce an autoimmune response leading to the development of RA. He testified that aluminum contained in the Gardasil vaccine[10] could be implicated in the development of RA, opining that as aluminum is "gobbled up" by white blood cell macrophages, the process can stimulate an immunostimulatory cascade. Tr. at 77. Dr. Roseff acknowledged, however, that this aspect of his opinion was based solely on a single article[11] published by Judicial Watch, an advocacy organization**,** rather than a verifiable scientific

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[7] An antigen is defined as "any substance capable, under appropriate circumstances, of inducing a specific immune response and of reacting with the products of that response, that is, with specific antibody or specifically sensitized T lymphocytes, or both." *Dorland's Illustrated Medical Dictionary* 103 (32d ed. 2012) [hereinafter *Dorland's*].

[8] Dr. Roseff admitted that he did not know what particular amino acid chain was relevant in triggering the autoimmune response that he alleges could have caused Ms. Sullivan's RA. Tr. at 80.

[9] A proteome is defined as "the complete set of proteins produced from the information encoded in a genome." *Dorland's* at 1535.

[10] "Gardasil itself contains 225mcg of aluminum." Pet'r's Ex. 35 at 8. Aluminum acts as an adjuvant in the Gardasil vaccine (similar to many other common vaccines), meaning that it is a substance that enhances the body's immune response to an antigen. *See Dorland's* at 32 (defining adjuvant).

[11] Judicial Watch Special Report: *Examining the FDA's HPV Vaccine Records – Detailing the Approval Process, Side-Effects, Safety Concerns and Marketing Practices of a Large-Scale Public Health Experimen*t (June 30, 2008) (ECF No. 65-2) (Pet'r's Ex. 35) [hereinafter "Judicial Watch"]. The Judicial Watch article notes that unspecified testing reports showed that Merck had tested the Gardasil vaccine against an aluminum-containing placebo, and the authors of the article argue that "[u]sing a reactive aluminum-containing placebo instead of a non-reactive saline base can make vaccines seem safer than they may actually be." Judicial Watch at 8. The Judicial Watch article further indicated that the Merck study had identified a difference in terms of initial side effects (such as injection site reaction) among the ten percent of individuals who received

study.[12] *Id*. at 71-72, 78. Dr. Roseff cited no other literature supporting his assertion that aluminum in vaccines could cause injury. *Id.* at 79-80.

One factual issue that Dr. Roseff's opinion attempted to address was the lengthy time gap between when Ms. Sullivan received the three separate Gardasil vaccines (between June 27, 2007, and January 4, 2008) and when her symptoms actually began. (As noted below, after an onset hearing held by the prior special master presiding over this case, a fact ruling was issued determining that onset of Ms. Sullivan's illness occurred sometime in "late March or early April 2008, in the few weeks prior to April 18, 2008." *See Sullivan v. Sec'y of Health & Human Servs.*, No. 10-398V, 2013 WL 4011056, at *16 (Fed. Cl. Spec. Mstr. June 30, 2013) [hereinafter "Ruling Regarding Finding of Fact"]). Dr. Roseff acknowledged that the first time Petitioner sought care for her knee problem was on April 18, 2008, at which time she reported experiencing knee problems for only a week or two. Tr. at 44-45.

Dr. Roseff admitted that he could not distinguish which of three Gardasil vaccinations that Petitioner received was the primary cause of her RA, but argued that the build-up of all three vaccinations in her system could have been the instigating factor. Tr. at 69. However, he acknowledged that he could identify no particular study to support the conclusion that the series of Gardasil vaccines that Petitioner received could have had such a "cumulative effect." *Id.* at 85. Dr. Roseff also acknowledged that if the first vaccine that Ms. Sullivan received in June 2007 represented the beginning of this proposed build-up, the timeframe between her initial vaccination and onset of her alleged injury in April 2008 was greater than two months (*Id.* at 54), but he maintained that even the ten months between the first vaccination to onset would not be so long as to exonerate the Gardasil vaccination as having caused Ms. Sullivan's illness. *Id.* at 73.

To support his opinion regarding the lengthy temporal gap between vaccination and onset in this case, Dr. Roseff attempted to analogize Ms. Sullivan's circumstances to studies of other diseases featuring long latency periods, such as Lyme arthritis. Tr. at 23.[13] In the case of Lyme arthritis, exposure to an antigen (caused by a tick bite that introduces a bacterium into the body) can result in inflammatory arthritis with onset months after initial exposure. *Id.* The bacterium replicates in the

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what Dr. Roseff characterized as the "true placebo" (saline) versus other individuals who received the aluminum-containing vaccine. Tr. at 79. "By its own account, Judicial Watch is a 'non-profit, non-partisan, tax-exempt 501(c)(3) organization which as a public interest law firm specializes in deterring, monitoring, uncovering, and addressing public corruption in government.'" *Judicial Watch, Inc. v. U.S. Dep't of Justice*, 185 F. Supp. 2d 54, 57 (D.D.C. 2002).

[12] Indeed, Dr. Roseff admitted that he did not know whether the Judicial Watch article was authored by a doctor, or whether its conclusions or methodology were peer-reviewed by the scientific community. Tr. at 51. The authors of the Judicial Watch article themselves acknowledge that "Judicial Watch was not and is not interested in proving causality," indicating that "[o]nly science can do that." Judicial Watch at 20.

[13] For this aspect of his opinion, Dr. Roseff relied upon an article by Allen C. Steere & Lisa Glickstein, *Elucidation of Lyme Arthritis*, 4 Nature Reviews Immunology 143 (2004) (ECF No. 59-3) (Pet'r's Ex. 31). But when asked whether this study provided him with merely a hypothesis, or if in fact he believed that it was more likely than not that this is what happened to Ms. Sullivan, Dr. Roseff admitted that he did not know because the matter had not been studied adequately to answer the question. Tr. at 59.

individual's system, ultimately finding its way to the synovium (or the joint capsule) and causing an inflammatory arthritis which may persist despite successful antibiotic treatment of the infection. *Id.* at 23, 59. Molecular mimicry has been offered to explain the process by which this arthritic reaction occurs. Pet'r's Ex. 31 at 5. Dr. Roseff acknowledged, however, that this analogy was limited in its application. For individuals who develop Lyme arthritis, the bacterial infection has been found to be present in the joint capsule, and thus at the locus of the arthritis. Tr. at 24. By contrast, Dr. Roseff was unaware as to whether synovial biopsies had ever been conducted on individuals who had received the Gardasil vaccine and then developed RA, to see if, in fact, there was evidence of any components of the vaccine similarly present, acknowledging that the failure to find them present would greatly weaken his argument. *Id*.

Dr. Roseff went on to discuss another article addressing a case study that considered from a retrospective standpoint the records of ten lupus patients to evaluate the length of time in which each individual developed lupus after receipt of the Hepatitis B vaccine. *See* N. Agmon-Levin, Y. Zafrir, Z. Paz, T. Shilton, G. Zandman-Goddard & Y. Shoenfeld, *Ten Cases of Systemic Lupus Erythematosus Related to Hepatitis B Vaccine*, 18 Lupus 1192, 1194-96 (2009) (ECF No. 39-4) (Pet'r's Ex. 32) [hereinafter "Agmon-Levin"]. The researchers found that there was variable timing for onset of disease following vaccination, ranging from a few days to as long as a year, with an average time of onset around two months post-vaccination. *Id.* at 1193; Tr. at 27. Dr. Roseff opined that based on such results, Ms. Sullivan's initial development of knee symptoms about two months after exposure to her last Gardasil vaccine was a reasonable timeframe. Tr. at 28.

In addition, Dr. Roseff also cited an article evaluating a rise in an autoimmune form of diabetes (Type 1, insulin dependent diabetes mellitus ("IDDM")) in children in Finland following the introduction of the Hemophilus influenza B vaccine, finding an increase in the diagnosis clustering in a period starting at about the thirty-eighth month mark from the date of vaccination and lasting approximately six months. Tr. at 32; *see* John Barthelow Classen & David C. Classen, *Clustering of Cases of Insulin Dependent Diabetes (IDDM) Occurring Three Years After Hemophilus Influenza B (HiB) Immunization Support Causal Relationship Between Immunization and IDDM*, 35 Autoimmunity 247, 250-52 (2002) (ECF No. 59-2) (Pet'r's Ex. 30) [hereinafter "Classen"]. He also referred to a prospective cohort study which attempted to evaluate the possibility of an autoimmune response following annual influenza ("flu") vaccination in healthy adults by looking at the change in antibodies post-vaccination, using blood samples taken prior to vaccination and then at one month and six months post-vaccination. Tr. at 29-30; *see* N. Toplak, T. Kveder, A. Trampus-Bakija, V. Subelj, S. Cucnik, & T. Avcin, *Autoimmune Response Following Annual Influenza Vaccination in 92 Apparently Healthy Adults*, 8 Autoimmunity Reviews 134, 137-38 (2008) (ECF No. 59-1) (Pet'r's Ex. 29) [hereinafter "Toplak"]. While the flu vaccination generally did not alter the percentage of healthy adults with positive autoantibodies, the Toplak researchers found that six months post-vaccination, approximately thirteen percent of patients either had higher titers of antibodies or developed new antibodies. Tr. at 30; Toplak at 2. Dr. Roseff focused on the presence of antibodies and postulated that six months post-

exposure to a vaccination could actually be too soon to look for manifestations of clinical disease. Tr. at 30.

Dr. Roseff admitted that none of these studies involved the HPV vaccine generally (or the Gardasil vaccine more specifically), but justified his reliance on such studies in the absence of relevant, non-industry-funded, independent studies addressing the specific issue of RA following vaccination with Gardasil. Tr. at 33-34. Dr. Roseff also acknowledged that he knew of no persuasive epidemiologic or biologic evidence directly supporting his theory, but nevertheless opined "that it may just be too early to establish a statistical link." Roseff Report at 3. He maintained overall that there is "a strong possibility, knowing what we know about immunizations, and Gardasil specifically, that" the vaccinations that Ms. Sullivan received caused her RA. *Id*.; Tr. at 17.

In distinguishing reliable from unreliable studies, Dr. Roseff expressed the general opinion that studies sponsored by the pharmaceutical industry are inherently suspect due to bias. Tr. at 67 (referencing articles that he had read regarding bias in studies sponsored by the pharmaceutical industry); *see also* Joel Lexchin, Lisa A. Bero, Benjamin Djulbegovic & Otavio Clark, *Pharmaceutical Industry Sponsorship and Research Outcome and Quality: Systematic Review*, 326 BMJ 1167 (2003) (ECF No. 30) (Pet'r's Ex. 33) [hereinafter "Lexchin"]. He specifically questioned the scientific methodology of certain such studies. *See, e.g*., Tr. at 68. Thus, he opined that early studies sponsored by Merck, which did not observe harmful effects associated with the Gardasil vaccination, were tainted – both generally by Merck's involvement, as well as more specifically by the failure to use what he referred to as a "true placebo" group. *Id.* at 73. He testified that there were six initial studies conducted by Merck that purported to compare individuals who received the Gardasil vaccination to a placebo group, but only one study used a saline placebo (which Dr. Roseff deemed as the most scientifically reliable control) while most of the others used an aluminum-containing placebo (which he viewed as not a true placebo). *Id.* at 25. Dr. Roseff thus expressed the opinion that this group of studies was ultimately not reliable. *Id*. at 73.

2. *Dr. Carlos Rosé* – Respondent's expert, Daniel Carlos Rosé, M.D., graduated in 1977 from the University of Buenos Aires School of Medicine in Argentina, completing his residency in internal medicine at the University's hospital. Tr. at 87; Resp't's Ex. B. He then went on to an adult rheumatology fellowship in the National Institute of Rehabilitation; Department of Medicine, Rheumatology Division, Buenos Aires. Tr. at 87. In 1987, Dr. Rosé finished a pediatric residency at Thomas Jefferson University in Philadelphia, Pennsylvania, which was followed by a fellowship in pediatric rheumatology at Children's Hospital of Philadelphia. *Id.* Dr. Rosé is board-certified in pediatrics as well as pediatric and adult rheumatology. *Id*. He is currently a Professor of Pediatrics at Thomas Jefferson University where he teaches pediatric rheumatology to medical students, residents, adult fellows, and pediatric fellows, and he also lectures and publishes papers on the topic of RA. *Id.* at 89. He is a reviewer for several journals and on the editorial board for Rheumatology International. *Id.* at 89-90. He also serves on various Data Safety Monitoring Committees – also known as Data Safety

Monitoring Boards (which are committees of independent experts responsible for monitoring patient safety and treatment efficacy data during ongoing clinical trials).[14] *Id.* at 90.

Dr. Rosé has been treating rheumatology patients for over thirty years. Tr. at 88. Since 1989 he has practiced at the duPont Hospital for Children in Wilmington, Delaware, where he is currently the Head of Pediatric Rheumatology with supervisory responsibility over four pediatric rheumatologists. Tr. at 86-88. As part of his rheumatology practice, Dr. Rosé sees patients at least twice a week, ranging from infants to young adults. *Id*. at 88. Dr. Rosé diagnoses both RA and JRA because he sees patients up to eighteen years of age, and the relevant diagnostic criteria require a diagnosis of RA (rather than JRA) if onset occurred after the patient was sixteen years of age.[15] *Id.* at 90-91. On average, Dr. Rosé estimated that he sees approximately one hundred and fifty rheumatology patients per month. *Id.* at 88.

Relying on his experience treating patients with rheumatologic disease, Dr. Rosé formulated his opinion in this case after reviewing Petitioner's medical records, affidavits from Petitioner as well as her parents, and pertinent medical or scientific literature. Resp't's Expert Opinion Report dated Mar. 9, 2011 (ECF No. 19-1) [hereinafter "Rosé Report"] at 1; Resp't's Expert Opinion Supplementary Report dated Apr. 30, 2011 (ECF No. 19-1) [hereinafter "Rosé Supplementary Report"]; Tr. at 91-92. Based on this review, Dr. Rosé formed an opinion that it is more likely than not that the series of Gardasil vaccinations that Ms. Sullivan received were unrelated to the onset and development of her RA. Tr. at 92, 94.

Dr. Rosé began by providing an overview of arthritis generally, and RA more specifically. Dr. Rosé explained that RA is a disease of unknown etiology, with one hundred percent of cases being idiopathic. Tr. at 95. He indicated that RA is a uniform disease (although many rheumatologists distinguish between individuals with RA who are seronegative versus those who are seropositive).[16] *Id.* at 93. Dr. Rosé expressed the view that while infections can cause arthritis, most recent research identifies genetic factors, rather than environmental factors, as the most likely mechanisms associated with the development of RA (although he acknowledged that these findings may be influenced by the relative ease of studying such genetic factors as opposed to environmental factors). *Id.* at 96.

Dr. Rosé opined that there is no scientific or medical support for an association between the Gardasil vaccination and rheumatic disease. Rosé Report at 5-6. He indicated that although several

[14] Dr. Rosé is currently involved in two such committees, and he has experience dealing with both committees responsible for overseeing clinical trials funded by the pharmaceutical industry and committees responsible for overseeing non-industry sponsored clinical trials. Tr. at 90-91.

[15] Dr. Rosé noted an age distinction between RA and JRA – he indicated that the relevant diagnostic criteria put the age of onset of JRA up to sixteen years of age. Tr. at 88. Accordingly, Dr. Rosé indicated that rheumatoid conditions that begin when a patient is sixteen are not classified as juvenile. *Id.*

[16] Dr. Rosé indicated that seropositive individuals have rheumatoid factor or anti-CCP antibodies in the serum. Tr. at 94. Of those individuals who meet the diagnostic criteria for RA, eighty-five percent are seropositive, as was the case with Petitioner, and fifteen percent are seronegative. *Id.*

human infections have arthritis as part of their clinical presentation or are associated with the development of a rheumatoid-like disease, there are no known viral causes of RA. Tr. at 96. Moreover, the wild-type human papillomavirus is not a known cause of acute or chronic arthritis in humans – making it even less likely in his estimation that the Gardasil vaccine could be so associated. Rosé Report at 5-6; Tr. at 98. Although he acknowledged that the Gardasil vaccine contains viral particles from multiple strains of HPV rather than a single strain from the wild type infection, he maintained his view that it was unlikely that the Gardasil vaccine can cause arthritic conditions. Tr. at 99.

Dr. Rosé further testified that his view was supported by scientific and medical literature (or at least the absence of negating literature). Dr. Rosé opined that he could not find a single case of RA established to have been caused by the Gardasil vaccination. Tr. at 98-99. Moreover, he expressed the view that if such an association existed, he would expect to have seen it in his clinical practice, but never has. *Id.* at 98. Indeed, clinical trial data collected to date (from a safety database built with data from spontaneous reporting by those patients who participated in clinical trials and their treating physicians) on the development of autoimmune disease following receipt of a different formulation of the HPV vaccination[17] (as well as other vaccinations) illustrated that reporting rates of overall autoimmune events (including RA) did not differ between the vaccinated and control groups. Rosé Report at 3; Tr. at 99 (citing Verstraeten at 6631).[18] Dr. Rosé expressed the view that this is among the best evidence available regarding the vaccine's capacity (or lack thereof) to produce RA, as there currently are not (and may never be) any other case-control prospective epidemiological studies addressing this specific issue. Rosé Report at 3; Tr. at 99-101.[19]

Dr. Rosé went on to attempt to rebut Dr. Roseff's proposed mechanism by which RA could result after receipt of Gardasil. Although he agreed with Dr. Roseff's general characterization of the concept of molecular mimicry, he opined that there was no evidence that this mechanism is implicated in the development of RA; in fact, he indicated that it has not even been discussed in serious scientific or medical literature as a potential mechanism for the development of RA in at least the last ten years,

[17] This study involved a collection of "[a]ll completed or ongoing controlled, randomized studies of AS04 adjuvanted HPV-16/18, HSV and HBV vaccines conducted by GSK Biologics [GlaxoSmithKline, the manufacturer of those vaccines] or collaborators," with one exception. Thomas Verstraeten, et al., *Analysis of Adverse Events of Potential Autoimmune Aetiology in a Large Integrated Safety Database of AS04 Adjuvanted Vaccines*, 26 Vaccine 6630, 6631 (2008) (Resp't's Ex. A, No. 5) (ECF No. 19-6) [hereinafter "Verstraeten"]. This study collected data on vaccinations containing the AS04 adjuvant; Cervarix (as opposed to Gardasil) is the human papillomavirus-16/18 (HPV-16/18) vaccine from GlaxoSmithKline Biologics that contains this adjuvant. *Id.* at 6630. Thus, the research referenced in this article involves a different HPV vaccine than that at issue in this case.

[18] The "objective of this integrated analysis was to assess safety of AS04 adjuvanted vaccines with regard to adverse events (AEs) of potential autoimmune aetiology, particularly in adolescents and young adults." Verstraeten at 6630. It thus attempted to address the potential problem with smaller studies, which may not by themselves detect rare events. *Id.* at 6631.

[19] "Reporting rates of overall autoimmune events were around 0.5% and did not differ between the vaccinated and control groups. The relative risk (vaccine/control) was 0.92 [] in the HPV-16/18. Relative risks calculated overall, for disease category or for individual events were closer to 1, and all confidence intervals around the relative risk included 1, indicating no statistically significant difference in event rates between vaccine and control groups." Rosé Report at 3 (citing Verstraeten).

even though it was previously considered, a fact he attributed mainly to an evolving understanding of RA. Tr. at 104-05. He also emphasized that (as Dr. Roseff acknowledged in his expert report) the relationship between the development of anti-CCP antibodies associated with RA and their reactivity with host tissues is unclear (thus underscoring that the biological mechanism by which RA develops is not fully understood). Rosé Report at 4; Roseff Report at 3.

Dr. Rosé specifically took issue with the assumption that the existence of some homology between peptide chains in human tissue and the components of vaccines logically leads to the conclusion that an autoimmune process will occur. Rosé Report at 4-5; Tr. at 106-07. Dr. Rosé indicated that short peptide homology, referenced in the Kanduc article relied upon by Dr. Roseff in formulating his opinion, "is at most a hypothesis generation step towards a theory of molecular mimicry." Rosé Report at 4. Moreover, he noted that because there are only a limited number of amino acids in nature that can be assembled in a limited number of ways to make proteins, it is not uncommon to find five amino acids that are homologous merely by chance. Tr. at 107. Dr. Rosé further testified that the Kanduc article made what he termed "extremely far-fetched statements" regarding potential side effects associated with receipt of the HPV vaccine, including setting forth (based on peptide homology) "a whole list of diseases that bear limited relationship with immune responses," yet even the authors had not suggested or concluded that receipt of the HPV vaccine would result in the development of RA. *Id.*

Dr. Rosé also questioned the logic of Dr. Roseff's opinion that the series of Gardasil vaccines that Ms. Sullivan received could have cumulatively resulted in the onset and development of her RA. Tr. at 108. Dr. Rosé noted that the vaccine contains only microdoses of aluminum insufficient in volume to have a negative effect in the body, while the protein components of the vaccine would themselves not accumulate in similar fashion (if at all). *Id.* at 108-09. Alternatively, Dr. Rosé asserted, if Dr. Roseff meant to argue that "more challenge"[20] posed by the additional Gardasil vaccinations served to overstimulate Ms. Sullivan's immune system, then her medical history did not support such a theory because there was no evidence in the treatment record of any instances in which Ms. Sullivan experienced a physiologic response (*e.g.*, a fever) following receipt of vaccination, as would be expected if the vaccinations were affecting her in this manner. *Id.* at 109.

Dr. Rosé then pointed out what he saw as deficiencies in Dr. Roseff's explanations for the lapse of time between Petitioner's receipt of the Gardasil vaccinations and her development of RA. Tr. at 97-98. As a general matter, Dr. Rosé acknowledged that there could be a variable period of time between a viral or bacterial infection (such as Lyme disease) and the development of some arthritic conditions. *Id.*

[20] Challenge-rechallenge is "a paradigm for exploring whether one substance caused an adverse reaction. Under this model, an individual who has had an adverse reaction to the initial vaccine dose (the challenge event) suffers a worsening of symptoms after a second or third injection (the rechallenge event)." *Viscontini v. Sec'y of Health & Human Servs.*, No. 98-619V, 2011 WL 5842577, at *22 (Fed. Cl. Oct. 21, 2011) (quoting *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 603 (2010) (quotations omitted)).

But he contested Dr. Roseff's assertion that such conditions were analogous to RA.[21] *Id.* at 97. Moreover, in the case of Ms. Sullivan, he opined that the approximately three-month span between the onset of her first symptoms (around April 2008) and the completion of her Gardasil series (January 4, 2008) seemed too lengthy not to allow for the possibility of some intervening event as the real cause. Rosé Report at 2, 6. In Dr. Rosé's view, a relationship between the Gardasil vaccine and Ms. Sullivan's RA would be conceivable only if the period were shorter – two to four weeks between onset and last vaccination. *Id.* at 6.

C. The Chao Study

The parties debated the evidentiary significance of an epidemiological study cited by Respondent in rebuttal of Petitioner's claim. C. Chao, et al., *Surveillance of Autoimmune Conditions Following Routine Use of Quadrivalent Human Papillomavirus Vaccine*, 271 J. Intern. Med. 193 (2012) (ECF No. 49-4) (Resp't's Ex. F) [hereinafter "Chao Study"]. This peer-reviewed observational study[22] analyzed a database comprised of the medical histories of approximately 189,000 California women (members of two of Kaiser Permanente's managed care organizations in the State) to determine whether the studied population developed a variety of autoimmune conditions[23] after receiving the Gardasil vaccine. Chao Study at 194. The study monitored individuals for 180 days (six months) after receipt of vaccine one, vaccine two, and vaccine three. Tr. at 100-01; Chao Study at 194-95. As vaccine three was given six months after vaccine one, the total duration of the study was twelve months. Tr. at 100-01; Chao Study at 194-95. The researchers compared the results of the studied vaccinated population with unvaccinated, similarly-situated individuals also enrolled with Kaiser Permanente in Southern California, in order to compare incident rate ratios for the identified autoimmune conditions. Chao Study at 194-95. Based upon the data reviewed, the researchers did not observe an increased risk of

[21] Dr. Rosé particularly distinguished Lyme arthritis from RA, noting that Lyme arthritis is a single joint disease with a living microorganism (a bacterium) present in a patient's joint, whereas in a case such as this a vaccine administered remotely in an arm allegedly produces inflammation in multiple joints throughout the body. *Id.* at 108. Dr. Rosé acknowledged that in the case of Lyme arthritis, approximately ten percent of children and approximately thirteen percent of adults experience arthritic inflammation despite no evidence of persistent bacterial infection. *Id.* at 131-32. But he characterized such inflammation not as a dormant/latent condition that hides or takes time to occur, but as a *persistent* condition that is treatment-resistant, existing even after the initial infection is successfully resolved with antibiotics. *Id.* at 133-34.

[22] In an observational epidemiologic study, researchers analyze groups of individuals who were exposed to a test agent, comparing them with groups not so exposed. Michael D. Green, et al., "Reference Guide on Epidemiology," in *Reference Manual on Scientific Evidence* 549, 555-56 (3d ed. 2011). The Chao Study investigators drew inferences about the side effects of Gardasil based on historic data, where the assignment of subjects into a treatment group (women who received the Gardasil vaccine) versus a control group (women who did not) was outside of the investigators' control. *See* Chao Study at 194.

[23] The diseases monitored in the study included rheumatologic / autoimmune disorders, including immune thrombocytopenia, autoimmune hemolytic anemia, systemic lupus erythematosus, RA, and JRA. Chao Study at 194.

developing RA (or other autoimmune conditions) following receipt of the Gardasil vaccine.[24] *Id.* at 196, 201; Tr. at 101.

While acknowledging that he did not have any special expertise in identifying conflicts of interest in scientific studies (Tr. at 62, 84-85),[25] Dr. Roseff asserted that the Chao Study was biased because it had been sponsored by a pharmaceutical company (Merck). *Id.* at 35-36. In support of his view, Dr. Roseff pointed to articles like Lexchin that in his opinion raised legitimate questions about the impartiality of such pharmaceutical industry-sponsored studies; the article cited selection of an inappropriate comparator to the product being investigated and publication bias as potential explanations for this bias. With regards to the Chao Study, Dr. Roseff specifically questioned the control groups utilized in the study, arguing that he could not ascertain whether it was a valid comparison to the group that received the Gardasil vaccine. Tr. at 35, 38-39, 84-85. He further noted that the rheumatologists who were reviewing the cases of patients who had received the vaccine were not blinded as to that fact – a discrepancy that he proposed could have introduced bias into the study's results. *Id.* at 36, 65. At the same time, however, Dr. Roseff acknowledged that the Chao Study set forth many steps that the researchers had taken to help ensure the independence of its results from its sponsor.[26] But in his opinion, a prospective, placebo-controlled, double-blinded study would provide far more persuasive evidence regarding the safety of the Gardasil vaccination. *Id.* at 85.

In response, Dr. Rosé argued that the factors cited in the article referenced by Dr. Roseff – inappropriate comparator to the product being investigated and publication bias – were not applicable to the Chao Study. For instance, he argued that the requirement that Merck publish the Chao Study's findings regardless of outcome lent credibility to its results. Tr. at 110-13, 117. Dr. Rosé also disputed the validity of Dr. Roseff's concerns regarding the study's control group. He noted that it would likely have been approved by the Food and Drug Administration ("FDA") in advance, and in fact appeared to him (from his own review of the Chao Study) that the control group had been carefully selected. *Id.* at 113-14. Further, Dr. Rosé contested Dr. Roseff's argument that the only possible persuasive study

[24] The database reviewed in the Chao Study identified only four cases of RA within the included vaccinated population, with a frequency of incidence calculated at 4.6 per 100,000 patients a year. Chao Study at 199 (Table 3). By contrast, there were 39 cases observed among the unvaccinated, with an incidence rate of 7.0 for 100,000 patients a year, yielding an incidence rate ratio of 0.71. *Id.*; *see also* Tr. at 102. Dr. Rosé explained that this ratio, which is below 1.0, suggests that there is no increase relative to incidence – meaning that the number of vaccinated individuals in the database population experiencing the subsequent onset of RA was statistically insignificant. Tr. at 102. Moreover, it appeared to Dr. Rosé from review of the Chao Study that the researchers had double-checked their results to ensure they had captured all cases of RA or JRA, further supporting the reliability of the findings. *Id.* at 103.

[25] In fact, Dr. Roseff admitted that he lacked the professional background and expertise necessary to intelligently critique the methodology of the study. *See, e.g.*, Tr. at 84-85.

[26] Thus, as part of the post-marketing surveillance of the Gardasil vaccine, Merck was required by the Food and Drug Administration ("FDA") to report the results of the study regardless of outcome. Tr. at 62-63; *see also* Chao Study at 194. Moreover, the study design and methodology were pre-specified, with the protocol specifically approved by the FDA as well as an independent board, and all of the data was collected and analyzed at the managed care consortium Kaiser Permanente rather than by Merck. Tr. at 63-65; *see also* Chao Study at 202-03. And after its results were written up, it went through a scientific peer review process in accordance with the protocol set up by the Journal of Internal Medicine (the journal in which the results of the study were published). Tr. at 65.

regarding the safety of the Gardasil vaccine (in terms of autoimmune side effects, such as RA) would be a prospective, placebo-controlled study using saline for the control group. *Id.* at 114. Because autoimmune diseases occur so infrequently, such a study would require depriving thousands of control group participants of a vaccine that has been demonstrated to be beneficial – an outcome Dr. Rosé deemed unethical. *Id*.

D. Other Evidence

Ms. Sullivan submitted four affidavits regarding the onset of her symptoms, including two from herself. *See* Pet'r's Exs. 1, 21. One of Petitioner's own affidavits indicated that prior to receipt of the Gardasil vaccinations she was "a healthy and active teenager," but after receiving the vaccinations she "began to experience chronic joint pain, joint inflammation, severe systemic body pain, problems concentrating, memory difficulties, headaches, and changes in [her] personality and temperament." *Id.* at 1. Petitioner's affidavits were supplemented by a daily self-health log (essentially a journal) in which she documented her daily symptoms beginning in January of 2010. *Id.* at 4-52 (Pet'r's Ex. A). Petitioner also submitted affidavits from her parents, Sandy and Dennis Sullivan, which included information regarding their understanding of the onset of her symptoms. Pet'r's Exs. 23, 24.

Both sides also offered substantial scientific and medical literature. Ms. Sullivan submitted eleven articles relied upon by Dr. Roseff in formulating an opinion in this case. Respondent cites certain literature submitted by Petitioner, as well as eleven additional articles, relied upon by her expert in formulating his opinion or rebutting Petitioner's expert.

II. Procedural History

Ms. Sullivan filed her Petition on June 28, 2010. Pet. at 1. In it, she specifically alleged that she suffers from chronic fatigue, severe joint and body pain, joint inflammation, cognitive impairment, headaches, numbness and tingling in her extremities, and irregular or heavy menstrual cycles which were all caused in fact by the HPV vaccine. *Id*. at 3-4. Since the filing of the Petition, Ms. Sullivan has alleged more specifically (and offered testimony during the hearing to this end) that her vaccination caused her to develop RA. *See, e.g.*, Pet'r's Pre-Hr'g Filing (ECF No. 54); Tr. at 17.

On September 27, 2010, Respondent filed her Rule 4(c) report denying that Ms. Sullivan was entitled to compensation. ECF No. 7. In the ensuing twelve months, Petitioner filed medical records and both sides submitted expert reports. Thereafter, in September of 2011, the special master previously responsible for this matter scheduled a hearing for January 24, 2012, to resolve factual issues regarding the onset of Petitioner's condition. ECF No. 26.

The onset fact hearing was held as scheduled, with both sides filing pre- and post-hearing memoranda. That hearing included testimony from Petitioner plus her mother and father. *See* Ruling

Regarding Finding of Fact at 7. After completion of the hearing and the passage of additional time, the special master issued a Ruling Regarding Finding of Fact on June 30, 2013, determining as follows:

> Petitioner's onset of joint pain following her receipt of HPV vaccinations on June 27, 2007, August 26, 2007, and January 4, 2008, occurred somewhere between March and April 2008, in the few weeks prior to April 18, 2008, when she first visited her doctor complaining, inter alia, of pain to her left knee.

Ruling Regarding Finding of Fact at 19.

In light of the results of this ruling, the parties were directed to file supplemental expert reports incorporating the Court's factual determinations and evaluating to what extent, if any, their experts' conclusions were altered as a result. ECF No. 45. Those supplemental reports were submitted in the fall of 2013. The report submitted by Dr. Roseff indicated that the timing outlined in the Ruling Regarding Finding of Fact did not change his opinion regarding the role that Gardasil played in Ms. Sullivan's ultimate development of rheumatic disease (indicating that there are "precedents in the rheumatic diseases, or in the literature, that support a delay of several months (as opposed to weeks) between exposure to an offending antigen, and onset of disease"). Supplemental Expert Report by Dr. Roseff dated Sept. 16, 2013 (ECF No. 48-1) (Pet'r's Ex. 28) at 1.

In January of 2014, I was assigned to this matter, and I scheduled an evidentiary hearing for July 10, 2014. ECF No. 53. The parties made additional pre-hearing filings and then participated in the hearing as scheduled, concluding the proceeding in a single day, and filing no post-trial briefs. The matter is now ripe for resolution.

III. Applicable Legal Standards

To receive compensation under the Vaccine Program, a petitioner must prove either: (1) that she suffered a "Table Injury" – i.e., an injury falling within the Vaccine Injury Table – corresponding to one of the vaccinations in question, or (2) that her illness was actually caused by a vaccine (a category of claim often generically referred to as a "non-Table Injury"). *See* §§ 300aa-13(a)(1)(A),11(c)(1); § 300aa-14(a), as amended by 42 C.F.R. § 100.3; § 300aa-11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs*., 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs*., 440 F.3d 1317, 1320 (Fed. Cir. 2006).[27] No Table Injury is alleged in this case, so Ms. Sullivan must prove causation-in-fact.

[27] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit decisions are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd*, 104 F. App'x 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

Petitioners bear the burden of demonstrating actual causation by preponderant evidence. *Cedillo v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); § 300aa-13(a)(1). To do so, a petitioner must provide: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005). The preponderance standard requires a petitioner to demonstrate that it is "more likely than not" that the vaccine at issue caused her injury. *Moberly*, 592 F.3d at 1322 n.2. Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs*., 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs*., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs*., 451 F.3d 1352, 1355 (Fed. Cir. 2006). To determine if the petitioner has carried her burden, I must assess "the record as a whole" and may not make an entitlement decision in her favor based solely on her own claims "unsubstantiated by medical records or by medical opinion." § 300aa-13(a)(1).

Each of the *Althen* prongs requires a different showing (although the preponderant evidence standard applies to each). Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 549.

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Andreu*, 569 F.3d at 1380; *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (a petitioner "must do more than demonstrate a 'plausible' or 'possible' causal link between the vaccination and the injury; he must prove his case by a preponderance of evidence") (citations omitted).

Often, however, establishing a sound and reliable medical theory requires that the parties present expert testimony in support of their claims. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc*., 509 U.S. 579, 594-96 (1993). *Cedillo*, 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether

a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

In other federal judicial fora (such as the district courts), the *Daubert* factors are employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to determine the persuasiveness of expert testimony has routinely been upheld. *See, e.g.*, *Snyder v. Sec'y of Health & Human Servs*., 88 Fed. Cl. 706, 742-45 (2009). In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead is employed to determine whether expert testimony offered is reliable and/or persuasive.

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In this regard, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the

treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records setting forth a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. § 300aa–13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder*, 88 Fed. Cl. at 746 n.67 ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). Rather, as with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record – including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Dep't of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (2011), *aff'd*, 463 F. App'x 932 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id*. at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. denied after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 2013 WL 1896173 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review denied* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

IV. Analysis

I find, based on the existing record and testimony at hearing, that Ms. Sullivan has not met her burden of proof with respect to any of the *Althen* prongs.

A. *Althen* Prong One

At the outset, I note that Dr. Roseff's testimony on the "can cause" *Althen* prong one required him to go beyond his immediate professional expertise in the field of rheumatology. By his own

admission, Dr. Roseff is not an immunologist, and has no demonstrated experience evaluating the effects of *any* vaccines in causing injury, in his own medical practice or elsewhere.[28] And he did not ground his proposed theory for how the vaccine could have resulted in RA with any reference to his own professional experience (such as a study or experiment he participated in, or article he authored, relevant to such testimony).

I have heard and considered Dr. Roseff's testimony despite the above. However, I may take into account an expert's overall competence in the field upon which he testifies as part of my weighing of the evidence. *See, e.g.*, *Walton v. Sec'y of Health & Human Servs.*, No. 04-503V, 2007 WL 1467307, at *17-18 (Fed. Cl. Spec. Mstr. Apr. 30, 2007) (otolaryngologist not well suited to testify about disciplines other than her own specialty). Dr. Roseff's lack of expertise on the topic of the capacity of vaccines such as Gardasil to cause injury leads me to give his testimony less weight than I might give the testimony of an expert with greater demonstrated experience in the subject matter. *See, e.g.*, *King v. Sec'y of Health & Human Servs.*, No. 03-584V, 2010 WL 892296, at *78-79 (Fed. Cl. Spec. Mstr. Mar. 12, 2010) (petitioner's expert far less qualified to offer opinion on general causation issues pertaining to autism than specific issues pertaining to the petitioner's actual medical history, given the nature of the expert's qualifications).

Putting that aside, I find that the substance of Dr. Roseff's opinion was unpersuasive and not supported by reliable evidence. He referenced no studies in which the Gardasil vaccine, any other HPV vaccination, or even a single strain of HPV wild virus, has caused RA (or any disease comparable to RA). Instead, he attempted to develop his theory by way of analogy to studies involving arthritic conditions arising after exposure to different viruses (such as the rubella virus or human parvovirus), or studies (like Toplak) observing autoimmune responses after vaccination. *See supra* Section IB1 (outlining Dr. Roseff's testimony). In effect, Dr. Roseff argues, (a) other viruses can produce arthritic conditions, and (b) vaccines can cause autoimmunity, therefore (c) it is reasonable to conclude by means of extrapolation from such evidence that the Gardasil vaccine could cause RA.

Although there is logic to such reasoning, I do not find that the evidence upon which it is based is sufficiently reliable to bulwark Petitioner's causation theory with the needed evidentiary ballast. As another special master noted in considering the *Althen* prong one analysis, "[t]he weight to be given an expert's opinion is based in part on the size of the gap between the science and the opinion proffered." *Isaac v. Sec'y of Health & Human Servs.*, No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for review den'd*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 Fed. App'x 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 at 1339). Here, that gap is too great. The fit between the literature Dr. Roseff cites and the theory he proposes is poor, based on inapposite comparisons involving different

[28] Admittedly, Dr. Rosé similarly lacked such qualifications. Because Petitioner bears the burden of proof, however, it is especially important that an expert testifying on her behalf possess sufficient credentials and expertise upon which to base his opinion. *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1317 (9th Cir. 1995) (indicating that "[o]ne very significant fact to consider is whether the experts are proposing to testify about matters growing naturally and directly out of research they have conducted independent of the litigation, or whether they have developed their opinions expressly for purposes of testifying").

vaccines and different illnesses or untestable premises. Dr. Roseff assumes, without demonstrating, that other viruses that have been scientifically observed to produce arthritic conditions are comparable not only to the HPV wild virus but to the Gardasil vaccine itself (which contains four HPV strains). He also conclusorily reasons that a generalized reaction to one kind of vaccine is comparable to the type of reaction that one would expect to see from an entirely different vaccine. And in some cases, (specifically, with regard to the Classen article purporting to identify a causal link between other vaccines and IDDM), he relies on literature directly relating to theories that have been routinely rejected when offered to establish causation involving the tested vaccine. *See, e.g.*, *Meyers v. Sec'y of Health & Human Servs.,* No. 04-1771V, 2006 WL 1593947, at *5 (Fed. Cl. Spec. Mstr. May 22, 2006) ("[t]his court has previously considered and discredited the theories advanced by Dr. Classen") (discussing *Baker v. Sec'y of Health & Human Servs.*, No. 99-653V, 2003 WL 22416622, at *33 (Fed. Cl. Spec. Mstr. May 22, 2006)).[29]

Ms. Sullivan's overall theory regarding how the Gardasil vaccination could cause RA fails to hold up when analyzed under the *Daubert* framework used to evaluate the reliability of expert testimony in Vaccine Program cases. It has not been tested, subjected to peer review, or shown to be generally accepted in the relevant medical community. *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95). While some of the individual pieces of literature cited by Petitioner may meet those criteria, that does not mean that Petitioner's overall theory (in support of which they are cited) is similarly reliable. In addition, (as noted above) nothing about Petitioner's theory is derived from Dr. Roseff's personal expertise, further diminishing its reliability (since he is the theory's author). And in many instances Dr. Roseff (who appeared to me an honest witness) undercut his opinion with admissions that Ms. Sullivan's illness may just as likely be of unknown origin. *See, e.g.*, Roseff Report at 3 (indicating that "we cannot exclude the possibility that her development of disease was a random event," and admitting that "how [molecular mimicry] could result in our patient's CCP positivity is unclear").

The same considerations apply to Dr. Roseff's proposed molecular mimicry mechanism. A petitioner may successfully establish causation without proving the mechanism of injury. *Knudsen*, 35 F.3d at 548-49 (citations omitted). And there are Vaccine Program decisions in which molecular mimicry has been found to be a scientifically acceptable explanation sufficient to meet the preponderant, "more likely than not" evidentiary standard. *See, e.g.*, *Tompkins v. Sec'y of Health & Human Servs.*, No. 10-261V, 2013 WL 3498652, at *22 (Fed. Cl. Spec. Mstr. June 21, 2013) (in the specific context of establishing causation of Guillain-Barré syndrome after vaccination, "[t]he molecular mimicry theory is the one most widely accepted for the agents most frequently accepted as causal"), *mot. for review denied*, 117 Fed. Cl. 713 (2014); *but see Wirt v. Sec'y of Health & Human Servs.*, No. 11-118V, 2014 WL 1911421, at *9-10 (Fed. Cl. Spec. Mstr. Apr. 18, 2014) (petitioner failed

[29] The special master's decision in *Baker* specifically discussed the weaknesses of the Classen article cited by Dr. Roseff herein. *See Baker v. Sec'y of Health & Human Servs*., No. 99-653V, 2003 WL 22416622, at *11 (Fed. Cl. Spec. Mstr. May 22, 2006).

to satisfy *Althen* prong one in case in which expert proposed molecular mimicry as a mechanism by which the HPV vaccine could cause RA).

A petitioner cannot, however, simply intone the phrase "molecular mimicry" and thereby be deemed to have satisfied her *Althen* prong one burden. *Hennessey v. Sec'y of Health & Human Servs*., 91 Fed. Cl. 126, 134-35 (2010) (noting expert's overly broad application of the molecular mimicry theory made it meaningless). Here, and for the same reasons stated above, Petitioner has not sufficiently connected this aspect of her causation theory to the Gardasil vaccine or her RA to be legally persuasive,[30] because she has not offered sufficient reliable proof supporting the concept in this particular factual context.

Petitioner offers a few alternative mechanisms, but they are incompletely sketched out at best. Dr. Roseff proposed that aluminum contained in the Gardasil vaccine (as an adjuvant) could be responsible for stimulating an individual's immune system in a destructive manner (and he ties this argument in with his criticisms of a Merck study that used a placebo containing aluminum). *See, e.g.*, Tr. at 25. Yet he admitted that this theory was highly speculative and based on very little scientific literature, if any. *Id.* at 60. Indeed, it appears from my review of the record that the only piece of filed literature even mentioning aluminum as a vaccine adjuvant, and the potentially negative impact it could have in causing a reactive disease or condition, is the Judicial Watch article – an advocacy piece with little scientific reliability, and which is conclusory in making this assertion as well. *Joiner*, 522 U.S. at 146 ("[t]rained experts commonly extrapolate from existing data[,] but nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert.").

Overall, Dr. Roseff has (by his own admission) done no more than opine that it is intellectually conceivable that administration of the Gardasil vaccine could result in the onset and development of RA. But this is insufficient to meet Petitioner's burden of proof, which (while not requiring scientific certainty) does obligate Petitioner to provide a "legally probable" explanation. *Moberly*, 592 F.3d at 1322 (quoting *Knudsen*, 35 F.3d at 548-49). Dr. Roseff's opinion, and the evidence offered in support of it, do not rise to that level of preponderant proof. *See also Wirt*, 2014 WL 1911421, at *9 (determining that "[t]here are simply too many unknowns, too many gaps in the analytical process of the theory, [] to conclude that Petitioner has proven a medical theory causally connecting the [HPV] vaccination and the injury [RA].") (citation omitted).

[30] There are also deficiencies with Dr. Roseff's explanation of homology within the context of the molecular mimicry process he proposed. Dr. Roseff relies on Kanduc for the proposition that one HPV strain of the four contained in the Gardasil vaccine shares peptide sequences with a variety of human proteomes, and therefore the cross-reactivity that would result in RA could conceivably occur. *See* Tr. at 19-20. But as Respondent pointed out, that HPV strain shares *numerous* sequences with the human body, perhaps too many to reach the conclusion that molecular mimicry would in fact occur resulting in RA. *See Id.* at 107. While the law does not require Petitioner to "prove" homology in a Program case, I take note of the fact that Respondent's challenges to this part of Petitioner's theory were not rebutted. *See, e.g.*, *Id.* at 80; Rosé Report at 4; Roseff Report at 3.

Also relevant to my analysis is the fact that Respondent offered credible and persuasive epidemiologic evidence – the Chao Study – undermining Petitioner's theory. Unquestionably, a petitioner need not offer epidemiologic proof to establish a reasonable and scientifically-reliable theory under *Althen* prong one. *Capizzano*, 440 F.3d at 1325. However, I may properly weigh such evidence against Petitioner's proof in evaluating whether she has carried her overall burden as to this first *Althen* prong. *Koehn*, 2013 WL 3214877, at *25 ("[t]he Federal Circuit has endorsed consideration of epidemiological studies as one factor in the special master's analysis");[31] *see also C.K. v. Sec'y of Health & Human Servs.*, 113 Fed. Cl. 757, 770 (2013) (a special master may evaluate contradictory evidence offered by Respondent).

The Chao Study is directly relevant to Ms. Sullivan's claim, and is persuasive evidence contradicting her causation theory. The same study has been determined in other Vaccine Program cases (in which it was invoked by Respondent) to be a valid epidemiologic study. *See, e.g.*, *C.K.*, 113 Fed. Cl. at 770; *Godfrey v. Sec'y of Health & Human Servs.*, No. 10-565V, 2014 WL 3058353, at *17 (Fed. Cl. Spec. Mstr. June 11, 2014); *Harris v. Sec'y of Health & Human Servs*., No. 10-322V, 2014 WL 3159377, at *13-14 (Fed. Cl. Spec. Mstr. June 10, 2014), *mot. for review denied*, __ Fed. Cl. __ (Sept. 23, 2014). Although the Chao Study is not proof positive (from a legal standpoint) that Gardasil does not "cause" RA (and indeed as a special master I am not empowered to make such a scientific determination), the Chao Study undermines Petitioner's case that "more likely than not" the vaccine could have that effect.

Ms. Sullivan endeavored to call into question the study's credibility by impugning its source. The argument that a given study's authorship might impinge on the reliability of its findings is reasonable. *See, e.g.*, *Harris*, 2014 WL 3159377, at *13 ("the source for Dr. Chao's funding opens a potential (if ultimately unresolvable) argument that her conclusions are not valid"). But the Supreme Court in *Daubert,* as well as the cases following it, has provided analytical tools for evaluating the existence of alleged errors in a study's methodology or analysis that, if present, would illustrate bias better than the unsubstantiated argument that an interested sponsor automatically casts doubt on the honesty of the study's findings. *Daubert*, 509 U.S. at 592-95.

Therefore, in order to put flesh on the bones of her argument that the Chao Study was biased, Petitioner needed to point out specific elements of the study demonstrating its unreliability. She failed to do so. The Chao Study simply looked at what actually happened to a large group of individuals who received the Gardasil vaccine versus those who did not, performing some subsequent statistical analyses to evaluate the significance of the incidence of autoimmune diseases after vaccination. An argument could be made that a larger sample size was needed to produce more reliable results, but Petitioner does

[31] On appeal, the Federal Circuit upheld the special master's finding in *Koehn* (which specifically considered the Chao Study) but found that he had misapplied the law in determining that the petitioner had not met her burden under the first *Althen* prong. *Koehn*, 773 F.3d at 1244 n.1. In so doing, however, the Federal Circuit did not call into question the special master's earlier statement on the evidentiary significance of epidemiologic evidence (when offered) in evaluating this prong of the *Althen* test, nor did it find that the manner in which he had evaluated the weight to be afforded the Chao Study was an element of the error it ruled he had otherwise committed.

not make that assertion. *Hart v. Sec'y of Dep't of Health & Human Servs*., 60 Fed. Cl. 598, 608 (2004) (quoting *In re Norplant Contraceptive Prods. Liab. Litig.*, 215 F. Supp. 2d 795, 830 (E.D. Tex. 2002)) ("epidemiological data that is not statistically significant cannot provide a scientific basis for an opinion of causation"). And the low incidence rate ratio for vaccinated individuals who subsequently developed RA (0.71) supports (at least from a statistical standpoint) the Chao Study's conclusion that Gardasil is highly unlikely to cause RA. *See Daubert*, 43 F.3d at 1321 (citing *DeLuca v. Merrell Dow Pharm., Inc*., 911 F.2d 941, 958 (3rd Cir. 1990)) ("[f]or an epidemiological study to show causation under a preponderance standard, 'the relative risk of ... [the defect or injury] arising from the epidemiological data . . . will, at a minimum, have to exceed '2'").[32]

Those criticisms of the Chao Study Dr. Roseff did raise, such as the adequacy of its methodological control group, were not backed up by reliable evidence. Dr. Roseff's complaint that a truly independent study of vaccine safety would have created a blinded control group to receive a "true placebo" (saline) amounts to the assertion that only a randomized control study is trustworthy, as opposed to the observational study set forth in the Chao Study. It may be true that a more scientifically certain (and therefore persuasive) study is conceivable, and it is also the case that observational studies have their own inherent flaws. *Dwyer v. Sec'y of Health & Human Servs.*, No. 03-1202V, 2010 WL 892250, at *64 (Fed. Cl. Spec. Mstr. Mar. 12, 2010) ("[e]very observational epidemiological study has some weaknesses because such studies examine the world as it is"). But (operating from the well-worn maxim that "the perfect is the enemy of the good")[33] the possibility of a *better* study is not an effective critique of an existing, otherwise valid study. *See also Harris*, 2014 WL 3159377, at *13 ("a perfect scientific study is not required by the relevant legal standards").

The only other proof that Ms. Sullivan offers to support her causation theories are VAERS reports and data from the Gardasil package insert – none of which are particularly persuasive evidence. Because of their passive nature and unverified claims, VAERS reports are too anecdotal and unscientific to have much probative value in establishing a causation theory.[34] Statements contained in

[32] The Chao Study's findings regarding the safety of the Gardasil vaccination are bolstered by the findings from Verstraeten, which compiled data from smaller clinical trials in an effort to identify a correlation between receipt of the HPV vaccination and the subsequent development of autoimmune disease when such data was aggregated (but finding no such association). *See* Verstraeten at 6630.

[33] This phase is attributed to Voltaire and is literally translated as "the best is the enemy of the good." *Bartlett's Familiar Quotations* 343 (125th ed. 1980).

[34] As another special master has commented in connection with the evidentiary value of VAERS reports,

> VAERS is a stocked pond. It only contains reports (many of which are unverified or incomplete) of adverse events after vaccinations. VAERS contains no reports or data about the relative rate of these same events in individuals who have not been vaccinated. Thus, the number of specific adverse events, such as GBS, reported after any vaccine, is meaningless without information about the background rate of that adverse event and information about the number of vaccines administered.

Tompkins v. Sec'y of Health and Human Servs., No. 10-261V, 2013 WL 3498652, at *16 (Fed. Cl. Spec. Mstr. June 21, 2013), *review denied sub nom.*, *Tompkins v. United States*, 117 Fed. Cl. 713 (2014).

vaccine package inserts do not constitute reliable proof of causation, and cannot be deemed admissions that the vaccines in question have the capacity to harm a particular petitioner in a specific manner. *See Werderitsh v. Sec'y of Health & Human Servs.*, No. 99–319V, 2005 WL 3320041, at *8 (Fed. Cl. Spec. Mstr. Nov. 10, 2005) (quoting 21 C.F.R. § 600.80(l) as saying "[a] report or information submitted by a licensed manufacturer . . . does not necessarily reflect a conclusion by the licensed manufacturer or FDA that the report or information constitutes an admission that the biological product caused or contributed to an adverse effect").[35] The record is therefore insufficient to establish by a preponderance of the evidence Petitioner's theory that the Gardasil vaccine can cause RA.

B. *Althen* Prong Two

There is a notable lack of record support for the second *Althen* prong – that the Gardasil vaccine "did" cause Ms. Sullivan's injuries. Petitioner's contemporaneous medical records provide no evidence – such as a treating physician's statement, or a test result – supporting the view that the Gardasil series she had received was connected to her RA. There is only the fact that Ms. Sullivan received her last dose of the vaccine in January 2008, and then began to complain of knee-related pain no earlier than late March to early April of 2008 (as the Ruling Regarding Finding of Fact establishes).[36] Mere temporal association, without more, is insufficient to establish causation. *See Moberly*, 592 F.3d at 1323. Here, however, that is all the Petitioner can offer.

[35] In any event, as Dr. Rosé noted, the numbers reported on the Gardasil package insert which Dr. Roseff characterized as evidencing a "disturbing trend" merely represented raw data gathered through a self-reporting mechanism after the trial, and do not suggest anything regarding causality - a fact which Dr. Rosé illustrated by referencing other numbers in the Gardasil package insert regarding trials of the vaccine. Based on Dr. Roseff's same logic, such data would seem to suggest that there were *more* adverse events following receipt of a saline placebo than there were following receipt of the Gardasil vaccination. Rosé Report at 3; *See also* Roseff Report at 3.

[36] As noted above, the onset issue was the subject of a prior evidentiary hearing conducted by the special master previously assigned to the case, and I have incorporated her ruling in my decision. This fact determination does not serve as "law of the case" (a doctrine that applies more to prior legal determinations in a proceeding) that I must necessarily follow. *See generally Banks v. United States*, 741 F.3d 1268, 1276 (Fed. Cir. 2014) (indicating that law-of-the-case doctrine "posits that when a court decides upon a rule of law, that decision should continue to govern the same issues in subsequent stages in the same case") (quoting *Christianson v. Colt Indus. Operating Corp*., 486 U.S. 800, 815-16 (1988)). Indeed, I am no more formally bound by the onset proceeding than I would be bound by my determinations in a different case, the determinations of a special master in another case, or even a Court of Federal Claims decision. *Hanlon*, 40 Fed. Cl. at 630.

However, neither party asked me to reconsider the Ruling Regarding Finding of Fact prior to the entitlement hearing in this case, nor did Petitioner attempt to argue that newly-discovered or additional proof relevant to onset favored a different outcome. Moreover, Dr. Roseff submitted a supplemental opinion in which he applied the findings from the Ruling Regarding Finding of Fact but still determined that his original opinion was valid. Supplemental Expert Report by Dr. Roseff dated Sept. 16, 2013 (ECF No. 48-1) (Pet'r's Ex. 28) at 1. Given the above (plus the fact that the Ruling Regarding Finding of Fact is comprehensive and was the result of a proceeding in which both sides had full opportunities to present evidence), in the exercise of my discretion I find that it is appropriate to adopt the Ruling Regarding Finding of Fact herein. *See Pacific Gas & Elec. Co. v. United States*, 114 Fed. Cl. 146, 149 (2013) (when a successor judge is transferred a case in which a prior order has been rendered, the successor judge "should not overrule the earlier judge's order or judgment merely because the later judge might have decided matters differently," but should exercise his discretion in determining if circumstances warrant reopening the previously-determined issue) (quoting *United States v. O'Keefe*, 128 F.3d 885, 891 (5th Cir. 1997)).

During the hearing, both experts acknowledged this lack of record support linking Ms. Sullivan's vaccination to her RA. Aside from a single rheumatologist (who appears to have been merely recounting Mr. Sullivan's view that her RA was connected to the Gardasil vaccine), none of Petitioner's treating physicians ever identified Gardasil as a possible cause of her injury. Tr. at 74-75, 138. Dr. Rosé indicated that (based on his own ample experience diagnosing RA) he did not himself see anything in her treatment record that would support such a connection. *Id.* at 138. Dr. Roseff's expertise in rheumatology would have made him well-qualified to point out contrary evidence from the record (such as a test result that suggested a connection between the Gardasil vaccine and the development of Ms. Sullivan's symptoms, even if overlooked by a treating physician), but he admitted he could identify no such evidence either. *Id.* at 75. Petitioner has thus failed to offer preponderant evidence in support of the second *Althen* prong.

C. *Althen* Prong Three

As I explained above, Ms. Sullivan did not provide a reliable theory for how the Gardasil vaccine could cause RA. Accordingly, she cannot satisfy the third *Althen* prong either, since the adequacy of the proposed timeframe in which the Gardasil vaccine could have caused the Petitioner's injury must relate to the medical theory for how this would occur in the first place. *Bazan*, 539 F.3d at 1352; *Shapiro*, 101 Fed. Cl. at 542. But even if I had found that Petitioner had provided preponderant evidence in satisfaction of *Althen* prong one, I would still find that this third prong has not been similarly satisfied.

Petitioner inconsistently argued what was a medically acceptable timeframe for onset in this case – sometimes appearing to measure onset from the last in the series of three Gardasil vaccinations she received, while other times suggesting that the series in total had a "cumulative effect,"[37] compounding over time from the date of the first or second vaccine in the series. Neither argument was persuasive.

Measuring from the last Gardasil vaccination Ms. Sullivan received (January 4, 2008), the onset of her RA symptoms (beginning "somewhere between March and April 2008," as determined at the onset fact hearing) occurred ten to twelve weeks thereafter. Dr. Rosé proposed, however, that a reasonable timeframe in which *any* vaccine might conceivably cause some kind of arthritic condition

[37] During the hearing, Petitioner at times displayed confusion as to what timeframe she intended to try to prove in which the vaccination resulted in the onset of her RA. Her pre-hearing filings characterized it as a "three month period of time between the onset of symptoms and the vaccine" (Pet'r's Pre-Hr'g Filing (ECF No. 54)), which is consistent with the Ruling Regarding Finding of Fact. At certain points throughout his testimony, however, Dr. Roseff referred to a two-month latency period as an appropriate temporal relationship between vaccination and onset of Petitioner's symptoms. *See, e.g.*, Tr. at 28, 33. Dr. Roseff further muddied Petitioner's argument by indicating that it was not clear to him whether it was the first, second, or third vaccination (or even a "cumulative effect" of all three vaccinations) that ultimately caused Petitioner's RA. Tr. at 54, 73.

would be no more than two to four weeks.[38] Rosé Report at 6. Given the above, three months appears too long a timeframe in which onset could have occurred.

Ms. Sullivan attempted to substantiate three months as medically acceptable, pointing to literature showing purportedly analogous diseases that can be latent for that same period or longer. For instance, Dr. Roseff analogized RA to an inflammatory arthritic condition caused by Lyme disease (an insect-borne bacterial infection). Before being first recognized as a separate entity, Lyme arthritis was initially confused with early RA, so facially this comparison is not inapt. *See* Allen C. Steere & Lisa, Glickstein, *Elucidation of Lyme Arthritis*, 4 Nature Reviews Immunology 143 (2004) (Pet'r's Ex. 31 at 2). But Dr. Rosé persuasively argued that the timeframe for the development of Lyme arthritis was more logically attributed to persistence of inflammation (despite the otherwise successful treatment of the initial infection) rather than latent onset.[39] Tr. at 23-24, 131-34. For his part, Dr. Roseff admitted that he could not support the Lyme arthritis analogy with any comparable research involving RA. *Id.* at 24. Indeed, it appears to some extent that Dr. Roseff chose the Lyme arthritis analogy mainly because it provided an instance of "a long period between infection and development of inflammatory arthritis," rather than for its demonstrable scientific similarity. *Id.* at 58. Further, Petitioner cited no evidence suggesting that any component of the vaccine had ever been found in an RA patient's synovial capsules (in the same manner that the Lyme disease bacteria are found there).

The same is true for the other purportedly analogous cases (as referenced in the Toplak or Agmon-Levin articles) involving latency periods cited by Dr. Roseff. The main common ground those articles generally have with present circumstances is the fact that they display a delayed autoimmune response following receipt of a vaccine. Otherwise, they all involve different vaccines and different diseases, and thus cannot be assumed to be scientifically comparable to a sufficient degree to support the theory that Ms. Sullivan could have experienced delayed onset of RA-related symptoms months after any of the series of Gardasil vaccines that she received. Indeed, these pieces of literature themselves are far more limited in the scope of their conclusions (as Dr. Roseff himself specifically admitted with respect to the Toplak article (*see, e.g.*, Tr. at 47-48)). The Toplak article concludes with the specific observation that the flu vaccine did *not* "increase the percentage of positive autoantibodies in the general healthy adult population," even if some autoantibody increases were seen at certain temporal points after vaccine administration – increases having "no clear clinical significance." Toplak at 138; Tr. at 30.

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[38] Other Vaccine Program cases involving RA or similar arthritic illnesses have found this same general timeframe to be reasonable (although I do not adopt it as the "correct" one, or the only one a petitioner could ever prove). *Capizzano v. Sec'y of the Dep't of Health & Human Servs*., No. 00-759V, 2006 WL 3419789, at *11 (Fed. Cl. Nov. 8, 2006); *Doe/28 v. Sec'y of Dep't of Health & Human Servs*., 2009 WL 229665, at *20 (Fed. Cl. Jan. 21, 2009) (finding that petitioner has shown a medically appropriate time interval between receipt of the hepatitis B vaccine and her development of nonspecific arthritis where approximately one month elapsed between petitioner's third hepatitis B vaccination and the onset of her symptoms, and "[t]he interval was so strikingly appropriate that four of her treaters ascribed her condition to the vaccination").

[39] *See* Allen C. Steere & Lisa Glickstein, *Elucidation of Lyme Arthritis*, 4 Nature Reviews Immunology 143 (2004) (Pet'r's Ex. 31) (indicating that "10% of patients with Lyme arthritis develop persistent synovitis, which lasts for months or even several years after the apparent eradication of the spirochete from the joint with antibiotic therapy.").

Petitioner was also unable to establish preponderant evidence that the series of three Gardasil vaccinations she received could produce in concert the onset of her RA symptoms in the early spring of 2008. In an attempt to do so, she proposed (through Dr. Roseff's testimony) something along the lines of a "cumulative effect" or challenge-rechallenge theory – that Ms. Sullivan's successive vaccinations (whether due to build-up of aluminum in Ms. Sullivan's body, or simply from her system being primed immunologically) culminated in her initial knee symptoms and ultimate development of RA. But this theory was thinly substantiated and inadequately explained. The record shows absolutely no evidence that Ms. Sullivan experienced any reaction after receipt of the prior two Gardasil vaccines, as Dr. Rosé noted would be expected to have occurred if her immune system was being challenged after each successive vaccination. Tr. at 109; *see also Hall v. Sec'y of Health & Human Servs*., No. 02-1052V, 2007 WL 3120284, at *7 (Fed. Cl. Sept. 12, 2007) (a petitioner who suffered from a shoulder injury was entitled to compensation based on a challenge-rechallenge theory when petitioner received two doses of the hepatitis B vaccine and after each dose, she experienced problems in her shoulder within two weeks of the vaccination; the amount of time between the first vaccination and the start of her problems was more than the amount of time between the second vaccination and the start of problems; and the reaction to the second vaccination was also more severe). And as discussed above, Dr. Roseff himself did little more than speculate that it was possible that the Gardasil series Ms. Sullivan received could have built up in her body in some manner to result in her initial symptoms, supporting this speculation with unscientific literature like the Judicial Watch article rather than reliable scientific or medical proof. Petitioner thus did not establish that it was more likely than not that the total series of Gardasil vaccinations could cumulatively produce her initial symptoms two to three months after receipt of the final vaccination.

Conclusion

I have great sympathy for the suffering Ms. Sullivan experienced after receiving the Gardasil vaccinations. However, based on the records filed and testimony at hearing, I cannot conclude that she is entitled to an award of compensation in this case. The Vaccine Act permits me to award compensation only if a Petitioner alleging a "non-Table Injury" can show by medical records or competent medical opinion that the injury was more likely than not vaccine-caused. Here, there is insufficient evidence to support an award of compensation, leaving me no choice but to hereby **DENY** this claim.

In the absence of a timely-filed motion for review (see Appendix B to the Rules of the Court), the Clerk shall enter judgment in accord with this decision.

IT IS SO ORDERED.

/s/Brian H. Corcoran
Brian H. Corcoran
Special Master